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Integrating functional brain neuroimaging and developmental cognitive neuroscience in child psychiatry research

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Abstract

Objective—To provide an overview of clinical research aiming to develop a mechanistic understanding of brain dysfunction in child psychiatric disorders.

Method—Technological, conceptual and translational approaches relevant to the investigation of brain function in pediatric psychiatric illnesses are explored. Research in the area of pediatric bipolar disorder is used as a prototypic model illustrating the use of complementary techniques of functional magnetic neuroimaging and neurocognitive studies to identify abnormalities in neural circuitry function.

Results—Studies of bipolar youth indicate impairment in cognitive and affective neural systems and in the interface of these two circuits. This evolving field paves a future pathway for identifying diagnostic biomarkers for the disorder, providing tools for monitoring response to pharmacotherapy, examining illness-associated alterations in developmental trajectory, and facilitating the use of animal research for guiding the development of novel treatment strategies.

Conclusion—Studies of brain function in child psychiatry are establishing a platform of knowledge and methods that offer promise for revolutionizing both models of illness pathophysiology as well as future diagnostic and therapeutic practice.

Keywords

fMRI; child; bipolar; affect; cognition

Introduction

Understanding alterations in functional brain systems in pediatric populations with mental health problems is critical for a multitude of reasons. While it is now widely appreciated that these disorders are in fact “Brain Disorders,” understanding the complex brain dysfunction that underlies neuropsychiatric illnesses such as schizophrenia, bipolar disorder, autism and anxiety disorders in children and adolescents is still a work in progress. Mechanistic knowledge of functional brain systems and their alteration in clinical disorders offers promise to discern the nature of the links between genetic causality at the cellular level and clinical symptom manifestation that result from alteration in cognitive and affective functions.

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Improved mechanistic understanding of changes in brain function in pediatric disorders can be achieved by implementing two complementary methods of investigation: noninvasive functional magnetic neuroimaging (fMRI) techniques and behavioral neurocognitive studies. With fMRI, the data collected is an indirect representation of brain activation shown by an individual subject while performing a cognitive task. This can be examined by comparing activation in one task 'condition' (for example, seeing angry faces) relative to another condition (i.e., seeing neutral faces) in the same subject; or can involve comparing data across subject groups (i.e., contrasting the pattern of brain activation on angry face condition between patient and healthy control groups). When activation patterns in different conditions are compared, there is "no fixed or absolute baseline" and effects are reported as relative differences between data on one condition compared to another condition, so that the data from these kind of fMRI studies in essence represents a statistical interaction subject group and task condition. A recent advancement in this line of work is the use of pharmacological functional neuroimaging (phMRI) which is beginning to make significant contributions to our understanding of the ways in which drugs affect brain systems to bring about behavioral improvement, where the pre and post treatment patterns of brain activation are compared. Electrophysiological studies provide an additional tool for this work by the virtue of their high temporal resolution for investigating the functional dynamics of neural systems.

Given the rapid progress and innovation in these areas of research, and their potential impact on clinical practice in coming years, in this paper we aim to describe the evolution of several inter-related concepts and research strategies that have implications for future research and clinical practice. These concepts include: (1) The importance of understanding the brain as being comprised of multiple functionally organized circuits or systems, rather than isolated regions performing discrete functions; (2) The potential uses of clinical biomarkers for understanding disorders and monitoring response to pharmacotherapy; (3) The growing understanding of alterations in the developmental trajectory of functional brain systems in patients with onset of psychiatric illnesses in childhood, adolescence, and young adulthood; (4) The opportunity provided by understanding at the level of functional brain systems to facilitate a translational integration of animal and clinical research; and (5) The prospect of multi-modal approaches for studying brain and behavioral systems in parallel. In order to illustrate the development of these concepts in clinical research, we will use pediatric bipolar disorder (PBD) and, to a lesser degree, attention deficit hyperactivity disorder (ADHD) as examples. The reason for choosing these two disorders as prototypic disorder models is to illustrate the significant involvement of archetypic affective and cognitive brain circuits that are relevant to the symptoms of these illnesses and the persistent traits that remain evident after remission. For example, PBD patients show severe affect dysregulation with prominent elated or irritable mood often mixed with depression, rapid cycling episodes. Some of the associated cognitive problems such as inattention and impaired executive function appear to remain present with only modest recovery after symptom remission. Patients with ADHD present with prominent attentional problems, impulsivity and motoric hyperactivity. While there are overlapping cognitive problems between these two disorders, affective symptoms are relatively specific to PBD and do not manifest as core symptoms in ADHD. Both PBD and ADHD provide good models for describing strategies for interrogating brain function in a clinically relevant way. In this paper, conceptual understanding of fMRI and behavioral studies of cognitive and affective circuitry is laid out to illustrate how a model of brain function is being built in PBD. Ideas for new lines of research are raised such as mapping treatment effects on brain systems, understanding the functional circuits supporting symptoms versus clusters of symptoms that define diagnoses, tracking brain maturation and its implications for the manifestation of illness, and exploring alterations in brain function as allied endophenotypes in family members to identify those at genetic risk to develop illness. Further methodological approaches that could spearhead progress in child psychiatry research are discussed which include human brain mapping guided by more invasive and highly specific animal studies,

utilization of identical innovative and precise neurocognitive paradigms in parallel translational studies with patients and in animal models, event related designs in fMRI, multimodal imaging and pharmacogenomics.

I. Development of Functionally Organized Cognitive and Affective Brain Systems

Cross sectional and longitudinal neuroimaging studies in healthy^{1,2} and ill³ children and adolescents offer a roadmap for probing cognitive and affective regions of the brain. fMRI procedures used to probe functional brain systems quantify blood oxygenation level dependent (BOLD) signal changes in the brain. These BOLD signals reflect changes in regional cerebral blood flow to provide an indirect index of regional neural activity.⁴⁻⁶ Unlike structural MRI studies, functional MRI studies monitor changes in brain function over time during the performance of cognitive tasks. In effect, this procedure can be used like a stress test, similar to the use of a treadmill in cardiology. Progressively greater processing burden can be imposed by cognitive tasks evaluating specific systems such as memory and attention, and the brain response to these increasing processing demands can be evaluated.

Following a very active decade of research in cognitive neuroscience, the functional brain systems that support many different sensory, cognitive and motor processes have become well delineated. Using behavioral tasks that place focused demand on one of these systems (e.g. precise tests of attention systems, perceptual discrimination, memory or problem solving), the normal organization of functionally specialized brain systems supporting specific psychological processing demands have been defined with considerable resolution. While fMRI does not have the fine temporal resolution of neurophysiological studies (e.g., EEG), it provides exquisite spatial/anatomic localization of behaviorally-relevant brain function. In broad strokes, this method provides a noninvasive tool for examining the brain at work in order to study the mechanisms of the mind and probe their functional integrity in psychiatric disorders. In this kind of work, investigators choose paradigms tailored to probe the functional integrity of a specific cognitive or affective brain system. These fMRI studies can also help to scrutinize the association between cognitive and affective brain circuits by exploring patterns of brain activation as subjects execute paradigms that probe cognitive and affective circuits separately as well as simultaneously in an MRI scanner.

I.a. Cognitive Neuroscience—The field of clinical cognitive neuroscience in child psychiatry has focused heavily on processes supporting a child's ability to filter relevant information and suppress extraneous and irrelevant distractions, in part because of the relevance of these processes for ADHD.¹ Cognitive control mechanisms such as impulse control, and response inhibition while maintaining vigilance, have been tested using multiple versions of Stop-Go tasks in healthy youths⁷⁻¹¹ and patients with attention deficit hyperactivity disorder (ADHD),^{12,13} and more recently with PBD.¹⁴ In typically growing children, behavioral maturation in terms of cognitive control is correlated with more discrete and fine-tuned activation of cognitive circuitry and less diffuse activation, reflecting a reduction of processing in task-irrelevant brain areas.^{1,15,16} There is now growing evidence to show correlations between increasing prefrontal gray matter density,¹⁷ behavioral self control and the functional brain activation in healthy children as they perform cognitive control tasks in an MR scanner.¹⁸

One important and related concept in cognitive neuroscience that developed in recent years is the top-down model of attentional control over multiple psychological and brain processes. Multiple lines of work document that the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC) serve as higher cortical centers of cognitive control, including attentional control as one component of such processes, working in concert with cingulate cortex and the striatum.^{14,19,20} Disorders such as ADHD display abnormalities in

fronto-striatal systems in the form of decreased or increased neural activation during performance of attention-demanding tasks in prefrontal and dorsal anterior cingulate cortex (dACC) with a presence²¹ or absence of compensatory activation in a frontostriatal-insular network.²² Studies have yielded distinct results such as an increase or decrease in striatal activation based on the nature of the behavioral paradigms used to probe brain circuitry of interest, age of the patient group, and the disorder being investigated.

fMRI Studies Probing Cognitive Functions in PBD: At least three studies have shown decreased VLPFC activation in PBD patients, relative to healthy controls, in addition to increased activation in temporal lobe with attentional tasks.^{14,20,23} In contrast, the only significant exception among the cognitive neuroimaging studies that showed increased activation in the DLPFC and VLPFC in PBD patients relative to healthy controls is a study probing visuo-spatial memory.²⁴ With regards to subcortical regions, studies have shown increased putamen activation with a Stroop perceptual-response conflict task²⁰ and decreased striatal activation with a response inhibition task.¹⁴ These differences in effects observed in striatum may be explained by the specific task demands that elicit variable levels of dysfunction, and perhaps also by disorder specific abnormalities, drug effects or the age of study participants.

Behavioral Cognitive Studies: Sophisticated neurocognitive testing in a laboratory/office setting is a useful adjunct to fMRI studies because time permits (unlike the time constraints in scanner studies) a wider range of task parameters and control tasks to be employed. This approach has been used to characterize abnormalities in attention, executive function, and working memory among unmedicated ill and medicated euthymic narrowly defined PBD patients relative to IQ matched healthy peers.²⁵ Recent studies parsing out cognitive abnormalities in narrowly defined PBD patients showed greater cognitive inflexibility compared to a more broadly defined phenotypic group with severe affect dysregulation.²⁶ Innovative paradigms such as probabilistic response-reversal tasks exploring reward mechanisms in PBD patients showed that patients took a longer time to learn a newly rewarded behavioral response option.²⁷ Paradigms such as this implicate fronto-striatal systems subserving cognitive flexibility and brain systems supporting reward processing. These processes are fundamental for reinforcement based learning and the ability to learn to flexibly adapt to changing environmental circumstances.

In summary, across divergent tasks probing various cognitive domains, functioning in frontostriatal cognitive circuitry (Figure 1) that connects the DLPFC and VLPFC to the basal ganglia (i.e., specifically dorsolateral caudate and ventral striatum) has been shown to be affected in PBD. While we are able to build preliminary models of altered cognitive brain circuitry from these findings, several major challenges still remain. For example, available evidence suggests some overlap in circuits implicated in ADHD.²⁸ Such observations may lead clinicians to consider treating symptoms such as inattention linked to fronto-striatal dysfunction common to both the ADHD and PBD, rather than to target diagnosis-specific brain circuits which may overlap across disorders.

Certain limitations of work in this area are noteworthy, including small samples from specialized research clinics, patients with varying acute severity of illness rarely followed over time, patients taking varying medications with diverse and poorly understood impact on functional brain systems, and the use of cognitive behavioral paradigms that often probe overlapping rather than highly specific mental functions. Also, until tasks are well-validated in healthy samples to establish normative developmental progression, interpretation of group differences needs to occur with caution. More studies with larger samples replicating findings with diverse cognitive challenge paradigms, greater control of treatment effects on findings in patient groups relative to healthy subjects, and a better understanding of the normal range of

development in different functional brain systems are all needed to facilitate the transfer of progress in this area to direct patient care.

I.b. Affective Neuroscience—Following progress in the cognitive neurosciences, considerable progress has been made in the field of affective neuroscience. Studies in this area are of potentially great significance for mood disorders research. Using paradigms that probe affective circuitry, investigators are beginning to understand the functional role of different brain regions that are critical in affective circuitry such as the VLPFC, insula, perigenual anterior cingulate cortex, and amygdala.²⁹⁻³¹ What is becoming increasingly clear is the complex role of the VLPFC which serves as an important hierarchical control region for affect regulation and for integrating affective and cognitive control systems. The VLPFC (inferior frontal gyrus; BA 47 and 45) is coming to be understood as a crucial region modulating affective responses in subcortical structures, in addition to its role in attentional control and response inhibition demonstrated in ADHD, bipolar patients and healthy subjects.³²⁻³⁴

fMRI Studies Probing Affective Systems in PBD: The pathophysiology of affect dysregulation in PBD has been probed using a variety of facial stimuli. Passive viewing of emotional faces such as angry faces elicits increased amygdala activation in PBD patients relative to healthy peers, accompanied by decreased activation in the VLPFC.³⁰ Because the VLPFC is believed to be an important modulator of emotional responses in the amygdala, the decreased activation in the VLPFC is thought to reflect reduced top-down control of the amygdala with limbic hyper-responsivity as the consequence. Interestingly, in the same study, the posterior face processing circuitry, in which the occipital visual system provides input to the lateral fusiform gyrus and superior temporal sulcus responsible for processing facial emotions,³⁵ showed decreased activation in PBD subjects relative to healthy individuals. Therefore, analyses implicate two circuits that are relevant to affect regulation and facial emotion processing: the fronto-limbic affective circuitry modulating emotional reactivity and the face processing circuitry that is relevant to the facial emotion processing (Figure 1). Interestingly, there are strong connections between superior temporal sulcus and amygdala, linking these two circuits.³⁵

Another study reported greater VLPFC and amygdala activity in response to evaluating 'hostility' in neutral faces versus 'nose width' in PBD patients compared to healthy controls (HC).³¹ This discrepancy in VLPFC activation in these two studies may be due to the type of faces, i.e., emotional versus non emotional faces used as stimuli, with PBD patients having perhaps greater difficulty activating VLPFC to regulate responses to explicitly emotional faces. Emotional pictures of scenes have also been used to study DLPFC and VLPFC activation in PBD patients, and studies with these stimuli have demonstrated greater and more diffuse prefrontal activation in the patients relative to healthy youths.²⁴ These findings highlight the exquisite sensitivity of functional brain systems to subtle modification of psychological processing demands, and therefore of the need for using multiple psychological approaches for probing brain systems of interest in order to understand their pathological function in clinical disorders.

Behavioral Studies of Social Cognition: Social cognitive deficits in mood disorders include impaired facial emotion recognition.^{36,37} Bipolar youth have been shown to misinterpret happy, sad, and fearful expressions of both the adult and child faces.^{36,38} Subjects with PBD, regardless of clinical and treatment status, have been shown to have marked impairments in the ability to correctly identify emotionally intense happy and sad facial expressions, tending to misjudge extreme facial expressions as being moderate to mild in intensity — perhaps reflecting their altered internal anchors for what extreme emotions are like.³⁷ Subtle variations of happy or sad expressions may be harder to interpret in unmedicated and acutely ill patients than in treated euthymic patients. Overall, patients with a younger age of onset or with comorbid

ADHD have been found to be more impaired in processing emotions.³⁷ These studies are important in two ways. First, they demonstrate social cognitive deficits in PBD that may be the result of affective and cognitive deficits that have been elicited in fMRI studies. Second, they illustrate the detail required for interpreting experimental findings with regard to multiple critical factors such as age of illness onset, comorbid conditions and medication status, as well as psychological paradigm issues such as age of facial stimuli, and the type and intensity of emotions they convey. Further, new models are emerging in understanding the role of social cognition in children with empathic failures such as psychopathy and autism. Amygdala and related noradrenergic connectivity responsible for making stimulus-punishment associations necessary for successful socialization are thought to be disrupted in psychopathy where there is a failure to learn to avoid actions that will harm others and ultimately elicit punishment for oneself.³⁹ Paradigms are being developed to examine brain function during face processing, threatening stimuli, reward and empathy to test these models.⁴⁰

I.c. Interaction between Cognitive and Affective Systems—One of the more exciting directions for future research involves efforts to probe the interface between affective and cognitive processing that may allow us to understand how “thinking” and “feeling” that are part of daily activities interact and impact each other. Studies conducted in macaque monkeys, healthy humans, and PBD patients collectively suggest an interaction between cognitive and affective brain regions at three hierarchically organized tiers: (1) higher cortical interactions between DLPFC and VLPFC;⁴¹ (2) an intermediate level of interface between dorsal and ventral ACC (pregenual and subgenual)⁴² and (3) interaction at the subcortical level between dorsal and ventral striatum and amygdala.⁴³ For our purpose of understanding disease models, the evolving understanding of how affective and cognitive brain systems interact is especially important for a disorder such as PBD, where both cognitive and affective systems are known to be compromised. However, as cognitive and affective processes are examined across a host of disorders, it is more the rule than the exception that both systems are compromised in critical and clinically important ways.

fMRI Studies Probing the Interface Between Affective and Cognitive Systems: Our recently completed study investigating the relationship between affective and cognitive systems has helped clarify the interrelationship between relevant neocortical systems in VLPFC and DLPFC.⁴⁴ We examined euthymic unmedicated PBD subjects and healthy individuals using a task that required subjects to match the color of emotional words with one of the two colored dots that appeared below. In response to negative word matching, relative to neutral word matching, patients with PBD had less activation at the junction of the VLPFC and DLPFC (See Figure 2), and greater activation of bilateral pregenual ACC and left amygdala. This dysfunction at the interface of affective (VLPFC) and cognitive (DLPFC) regions was greater in response to negative word matching when compared to positive word matching. This study illustrates a strategy for examining the impact of different emotions on cognitive operations. A second study is in progress examining the impact of implicit/automatic versus explicit/direct emotion processing while performing a cognitive task. Using paradigms such as these, healthy human⁴⁵⁻⁴⁷ and animal studies⁴⁸ have studied the automatic and fast transfer of emotional aspects of stimuli from visual association cortex to the amygdala via the occipitotemporal association circuit⁴⁹ (Figure 1). The key difference between fast implicit processing and explicit conscious processing of emotion is that the latter involves elaborate perceptual analysis and cognitive processing of stimuli and relevant context. Parsing different emotional systems and processes along these lines is likely to be very useful for delineating the brain processes that are selectively affected in various disorders, and potentially how they are altered by treatment.

Behavioral Studies of Cognitive and Affective System Interactions: Consistent with clinical observation, laboratory studies demonstrate that frustration adversely impacts cognitive processing and behavior in children with PBD.^{50,51} The paradigm used in the Rich et al. studies consisted of three attention tasks: 1) Feedback with no contingencies; 2) Feedback with contingencies; and 3) Rigged feedback to induce frustration. Healthy subjects responded by showing decreased reaction time when contingencies were introduced, while PBD subjects showed impaired performance when contingencies were introduced suggesting deficits in their ability to adapt to changing reward contingencies.⁵⁰ In addition, frustration was associated with disrupted attention allocation in children with PBD. Using psychophysiological methods, Rich et al.⁵¹ demonstrated that children with a narrow-phenotype of PBD had reduced P3 amplitude (an electrophysiological response to stimulus novelty) than other children with mood dysregulation or healthy subjects, reflecting impairments in cognitive monitoring and attention allocation. Studies such as these suggest that reward processing brain systems such as medial and lateral orbitofrontal cortex, cingulate cortex and ventral striatum,^{43,52} may be implicated in PBD and therefore suggesting the need for future fMRI studies of reward systems and their brain substrate in this disorder. This orbitofronto-striatal circuit underlying reward processing system appears to differ from the dorsal and ventral circuits that connect the DLPFC, VLPFC and caudate/striatum that support the attentional system (Fig.1). Studies of reward based learning may be informative for the development of more effective methods of treatment that consider frustration intolerance or reward processing deficits in PBD as a target. Further, these findings suggest a neural basis for the clinical observation that imposing negative contingencies or punishment to control behavior in PBD patients often increases arousal and dysregulated affect and behavior.

In the end, findings drawn from pathophysiology-oriented studies conducted in mood disordered youth and adult patients,⁵³ animal studies,^{43,54,55} and human brain mapping studies in healthy adults^{56,57} have provided important advances in child psychiatry. While in many ways we are still in the early phase of this line of work, progress to date has begun to help clarify many important issues including: (1) The importance of top down control mechanisms on affective and perceptual processes; and (2) A broad functional differentiation of dorsal cognitive regions and ventral emotional regions in prefrontal cortex that interact in complex ways which are crucial for understanding symptom expression.

II. pHMRI Studies for Understanding Treatment Mechanisms

While we are beginning to understand the mechanistic function of affective and cognitive brain circuitry underlying the emotional and cognitive difficulties in PBD and other child psychiatric disorders, knowledge on how treatments alter functional brain systems is still limited. While an extensive animal and human literature has been informative about receptor-level and signal transduction effects of psychiatric medications, much less is known about drug effects on functional brain systems that ultimately mediate therapeutic effects.

The basic aim of pHMRI studies is to determine how affected neural circuitry function can be normalized over the course of pharmacotherapy to more closely resemble that of healthy individuals, or to otherwise compensate for disorder-related alteration in brain function. This work will also help differentiate neural system dysfunctions during the acute state of illness from the stable persistent deficits that likely represent trait factors associated with the disorder. Examining patients at baseline and after recovery, and comparing responders and non-responders, will provide crucial new information about the effects of illness state and treatments on brain systems, and potentially provide predictors of treatment outcome. For example, it is important to learn whether there is a reversal of prefrontal hypoactivation and heightened limbic reactivity after treatment with mood stabilizers in PBD patients. Better knowledge of these processes has obvious implications for guiding rational treatment development.

Knowledge of the functional operations of neural circuitry will not only help pinpoint problem areas that can be potentially corrected with treatment, but identify subgroups of patients for whom particular interventions are likely to be most helpful. We are currently studying the effects of antiepileptic agents such as lamotrigine and valproic acid as well as the second generation antipsychotic risperidone in this regard, to examine the mechanisms of action through which they alter neural circuitry function in responders and non responders with PBD.

There are two key procedural issues with the phMRI trials.

(1) Studying untreated patients is central for learning about illness-related alterations in functional brain systems, and as baseline data for clinical trials—

Psychiatric medications alter functional brain systems to change emotional and cognitive function — the very reason for which they are clinically used. Therefore, studies investigating pathophysiology of functional brain systems and behavior in disorders such as PBD are often best served by conducting studies with untreated patients where the picture is not clouded by effects of current treatment. Otherwise, it becomes difficult, if not impossible, to separate illness from treatment effects in data. Also, with baseline data from untreated patients, the effects of medications on brain and behavioral systems can be more easily identified, and differences in drug-induced changes on brain systems can be examined separately in treatment responders and nonresponders. It is possible to take children off medications for scanning in certain situations. In our previous studies,^{30,44} we were able to accomplish this when parents wanted to know how their children would fare medication-free after having been clinically stable on medication for a long period of time. This is a rare opportunity, and brings difficulties and complexities for clinical research programs, yet is feasible in larger programs where patients are in long term follow-up care. Another approach that has been widely used in “first episode” studies of disorders in young adult life has been to study patients who have only recently begun to display serious psychopathology before treatment is first initiated. This approach is also relevant for child psychiatry research.

(2) Importance of scanning matched healthy controls in parallel with patient studies—

In order to identify alterations in brain systems in an illness over time with fMRI or neurobehavioral approaches, it is crucial to gather data in parallel from matched healthy control subjects, although they do not receive treatment. There are essentially no existing norms for any fMRI task in terms of normative brain activation patterns, much less developmentally informed norms. This is an especially important issue for studies aimed at detecting change in neural systems with fMRI of patient groups after treatment. These studies require parallel assessment of matched healthy subjects to account for test/re-test issues such as “practice effects” that can alter activation patterns and cognitive performance over time for reasons that are unrelated to treatment effects.⁵⁸ This may include effects of experience with specific test stimuli and strategic learning about how to approach test items that may consolidate before or in the days after initial testing. If such effects are not considered, what appears to be a treatment effect in a patient group may in fact be a practice effect in behavioral and fMRI data.

III. Biologically Based Understanding of Illnesses: Symptom versus Syndrome

PBD may be best conceptualized in terms of pathophysiology as a complex syndrome with affect dysregulation, inattention, cognitive inhibition problems, and executive cognitive function abnormalities that are likely to result from separate disturbances in different brain circuits. Each of these disturbances may in turn be linked pathophysiologically to corresponding genetically- and biochemically-mediated mechanisms. Each of these clinical aspects requires attention during treatment, and developing a better understanding of the causes of alterations in each dimension is an active area of research in several laboratories. This has considerable promise for having great impact on clinical practice. The current pattern in clinical

practice is to consider disturbances in different domains to represent “comorbid” expression of different disorders in a given patient. Rather than evaluating and treating disturbances in affect regulation and inhibitory attentional control, clinicians are forced to commit to multiple diagnoses such as PBD and ADHD and then treat patients accordingly. With a comprehensive understanding of brain function and its abnormality in clinical disorders, targets of pharmacotherapy can be conceptualized with greater neurobiological specificity and precision. This level of understanding may lead to a shift in thinking from treating ‘multiple comorbid disorders’ to treating ‘multiple dimensions of deficit’ — something probably more common now in general practice than in clinical trials. The progress of knowledge about brain bases of psychiatric disorders is evolving rapidly, and has reached a level of maturity allowing us to test innovative and focused questions about models of pathology and treatment intervention. One effect of this evolution, in years to come, may be a development of diagnostic practice more geared to treating alterations in brain systems rather than utilizing DSM symptom-based categorical diagnoses to guide therapeutic practice. The increasing observations of shared biological abnormalities across disorders rather than a pattern of specific abnormalities being linked to specific clinical disorders suggests that clinical practice may evolve in this direction in coming years. Therefore, a better understanding of the clinical relevance of alterations in functional brain systems will be key to that progress. Invariably, pharmacotherapy can be effectively prioritized based on the type of symptoms present. For example, affective symptoms may need to be addressed prior to treating attentional problems, and diagnostic consideration of ADHD-comorbidity is not imperative to make these decisions. An important dimension to this issue is how the course of illness is influenced by brain development. For example, attentional symptoms may precede manic symptoms which may be conceptualized as simply ‘attentional problems’ or as a ‘diagnosis of ADHD.’ These symptoms may be an earlier manifestation of fronto-striatal abnormalities relative to the emergence of fronto-limbic abnormalities related to the time course of regional neurodevelopmental alterations. Also, independent of affective systems, brain maturation such as increasingly efficient recruitment of DLPFC by age 16 may resolve decreased attentional problems.⁵⁹ Further, the level of severity in any given circuitry function may be reflected in the severity of symptoms that may not resolve with brain maturation, and vary based on treatment response. Therefore, considering symptom-brain function association rather than diagnostic classification, one can perhaps more clearly evaluate and appreciate the plastic nature of brain function informing symptom presentation and treatment planning.

Further, while multiple studies in PBD and ADHD show statistically significant group differences characteristic of that disorder, the field is still not at the point where such patterns can be consistently identified in individual patients to a level where they can serve as a biomarker for either disorder. Moving away from diagnosis to strategies that seek to identify specific symptoms that are closely aligned to brain function may be the best approach for identifying biomarkers in the form of pattern of neural circuitry dysfunction.

IV. Advances in Developmental Psychology and Developmental Neuroscience

Understanding the evolution of illness diatheses in children and the earliest signs of illness expression needs to be nested in a solid understanding of the normal trajectory in the maturation of brain functions. The pace of anatomic and functional growth may be slower, skewed, completely arrested at a point, or qualitatively deviant in patient groups compared to their healthy peers. Therefore, a comprehensive understanding of the developmental trajectory in healthy youths, as a gold standard, is essential to map the pattern of deviance in at risk individuals, in prodromal states, and during early illness progression. These earlier changes can serve as a cluster of diagnostic markers and treatment targets, facilitating early recognition and more effective intervention.

Functionally, the prefrontal cortex, is one of the last regions in the human brain to attain an adult level of development, typically by age 15-16 years.^{1,4} The results of neuroimaging studies in healthy as well as psychiatrically ill individuals show more diffuse activation in children and young adolescents than adults,^{59,60} suggesting that functional refinement of computational specialization of neocortical regions continues to mature during this time. From a behavioral perspective, subjects continue to show improvement in response inhibition and working memory abilities through at least mid adolescence.⁵⁹ However, with regards to social cognition, there appears to be a dip in the ability to encode faces in pubescence when compared to the prepubescent or post pubescent period,⁶¹ an effect for which the underlying brain substrate remains to be clarified. Initial Pediatric fMRI studies demonstrate that the basic circuitry that supports the *capacity* to perform a task is established by childhood. Changes in the participation of frontal cortex and the ability to recruit widely distributed brain circuitry support increases in the *efficiency* of the cognitive control of behavior during adolescence. This pattern was observed in studies investigating the cognitive development of working memory and voluntary response suppression in health adolescents¹⁸ and has implication for the interaction between brain maturation, cognitive development and illness in terms of charting the relationship between capacity to perform a task and the efficiency with which brain circuitry can be recruited to perform that task in health and illness. Therefore, a developmental focus is imperative in mapping the arrest or deviance in cognitive processes as opposed to cross-sectional understanding. *Structurally*, there is also heterochronous development of cortical gray matter with developmental curves for frontal and parietal lobes peaking at around 12 and for the temporal lobe at around 16, whereas cortical white matter refinements continue until near age 20.² The average age of menarche is now at age 12 in the USA, and Tanners stage 4 (the final stage of pubertal status) is typically reached earlier than the structural and functional maturation of the brain. It remains to be established how the plastic trajectory of neurohormonal processes impact brain functional maturation in health and illness, and if indeed they are significantly associated.

V. Allied Phenotypes and Their Value for Family Genetic Research and Early Detection of Illness Risk

Etiological heterogeneity and syndromal psychiatric diagnoses have been two factors that in combination have slowed progress in psychiatric genetics. For this reason, there has been growing interest in exploring allied phenotypes such as cognitive and affective circuitry dysfunction in family association studies. These biological phenotypic disturbances are hoped to be more tightly regulated by relevant genetic factors than overt illness expression, and therefore be more useful in elucidating the role of genetic factors in illness risk. The fundamental underlying principle of this view is that the genetic penetrance at the level of an intermediate phenotype is stronger and is potentially detectable even in healthy individuals who carry disease susceptibility genes.⁶² However, in order to demonstrate such effects, some cognitive tasks will be more useful than others by way of narrower genetic control, higher heritability, closer association with familial risk and superior psychometric characteristics as intermediate phenotypes.⁶³ Much work is ongoing to develop and contrast potential intermediate phenotypes for this purpose. This line of investigation is particularly attractive for child and adolescent psychiatric illnesses where genetic effects on cognition and physiology are not yet confounded by the long term use of medications, chronic illness effects or substance abuse. Based on existing studies of early onset schizophrenia and bipolar disorder, commonly affected cognitive domains across both disorders included attention, working memory, verbal memory and executive function in probands and their families, while motor problems were more specifically associated with schizophrenia.⁶⁴⁻⁷³ There is a strong tradition of cognitive research in schizophrenia and of affective research in bipolar disorder, although disturbances in affective and cognitive systems are implicated in these disorders. Therefore, investigators now are actively examining both cognitive and affective paradigms in studies of both disorders.

This is being done in order to maximize the utility of allied phenotypes in early onset illnesses in order to identify shared and separate risk factors for various disturbances in functional neural circuits that are associated with these conditions and that may be treatment targets regardless of the disorder in which they are seen.⁷⁴

An alternative model for studying allied phenotypes is using a high-risk strategy where a feature such as attentional function is tracked as a clinical problem prior to the conversion to PBD along with the option of examining the potential markers in unaffected family members. However, the best place to begin enquiry along these lines is to learn more about deficits in affected patients. The most promising parameters reaped from these studies can then be pursued in a second phase of work where family members can be examined for the presence of allied phenotypes.

VI. Translation of Research from Animal and Postmortem Studies to inform Systems Neuroscience Models in Clinical Research

With parallel advances in molecular and clinical neurosciences, for which systems neuroscience approaches provide a natural bridge, we stand to reap many benefits from translating animal study findings to the clinic. This approach offers fine grained functional characterization based on single neuron recording studies during ongoing behavior, and studies of drug effects on single neuron function, and characterization of gross anatomy and patterns of white matter connectivity not possible with humans. For example,⁴¹ studies of Walkers's area 12⁷⁵ and the ventrolateral convexity of the PFC in Brodmann's Areas (BA) 45 and 47 of macaque monkeys have shown that each receive strong inputs from limbic areas. This information has been crucial for developing models of top-down control from prefrontal cortex to limbic areas. The frontal mid-ventrolateral area of the PFC⁷⁶ appears to be an important junction where inputs from dorsolateral executive systems are coupled and integrated with emotional processing systems.⁴¹ The area at the junction of DLPFC and VLPFC, by integrating processing of cognitive and affective dimensions of immediate circumstances, is believed to be involved in top-down regulation of the amygdala, and thereby playing an important role in emotional modulation, providing information about anticipated and past reward and punishment for guiding future behavior.⁷⁷⁻⁷⁹ DLPFC (BA 9 and 46) is involved in processes such as shifting attention, working memory, and response inhibition, and is involved in the regulation of emotional responses in a context dependent manner via its rich connectivity to the medial PFC.⁸⁰⁻⁸² This systems-level understanding of prefrontal circuitry in relation to emotional processing provides an important framework for understanding the brain system abnormalities that cause dysfunctional cognitive and affective brain circuitry in child psychiatric disorders.

VII. Neurocognitive and Neuropsychology Approaches

Both sophisticated new methods of cognitive neuroscience and the traditional methods of clinical neuropsychology provide important tools for child psychiatry. Neuropsychological tests are well-normed, there is wide clinical experience in their use for clinical interpretation, and they are useful in predicting level of function in academic and social settings. In contrast, new paradigms from cognitive and affective neuroscience that are used in both human and animal models often have the advantage of being more easily being linked to specific neurotransmitter systems and precise functional brain circuits.

Developing neurocognitive tasks is an ever-evolving effort. Rather than seeking stability and standardization and established norms as is the case in clinical neuropsychology, these paradigms used for fMRI are continuously being altered to take advantage of animal work and computational neuroscience to establish more sensitive and specific tests for evaluating brain systems of interest. Constant challenges in developing neurocognitive tasks include optimizing

the difficulty of tasks for populations of interest to avoid problems of a task being too easy or having a task difficulty that surpasses the ability of individuals with the disorder or in the age range of interest. Newer tasks that utilize computer adaptive testing approaches to administer items in the range close to the peak ability level of each subject are currently being developed. Often, for clinical studies, combining tools of clinical neuropsychology and cognitive neuroscience can provide the most broadly useful strategy to take advantage of the benefits of both approaches.

VIII. Functional Imaging: Methodological Strategies

Block versus Event-Related fMRI Studies—In early fMRI studies, block designs were almost universally used for examining functional brain systems. In block design studies, which still provide more power for detecting effects of interest and remain the ideal approach in certain circumstances, individuals alternate between performing two or more task conditions — often a task condition during which activation of interest is believed to occur over a 20-30 sec period of task performance and a rest condition of a similar duration. As higher field magnets and faster rates of image acquisition became available to increase signal to noise ratios in fMRI studies, and statistical tools were developed for modeling the time course of response to tasks at the individual trial level, event related studies have become widely used. In event related studies, neural activation is modeled separately for each trial. This has advantages for contrasting trials of a different type (such as when subjects are exposed to positive or negative emotional stimuli, or during Go versus No-Go trials, or in successfully performed trials vs. error trials).

Functional Connectivity Analyses—In fMRI studies, activation is typically seen in multiple components of defined neural circuitry. When a novel task is being used for which relevant anatomic patterns of connectivity are not known, or when one is interested in assessing the level of functional connectivity across brain regions of interest, a useful approach has been to conduct what is called an “effective connectivity” analysis to evaluate the relationship between activation across brain regions responsible for a cognitive or emotional processing demand of interest. Often, this is done using a “seed” voxel (a 3 dimensional pixel, or volume unit in image data) in one ROI that is then correlated with all other voxels in the brain to define activation circuits in an exploratory manner. Principal component analysis and path analysis can be used for this purpose.

Age normed template—Creating an age appropriate template from the structural images of a matched healthy comparison group often can serve as a useful approach for defining anatomic regions of interest for a study in which subjects are young enough that gross development of brain anatomy is not complete. This averaged data from healthy subjects can serve as the study specific template to warp the data from each individual subject into common stereotactic space.

Reducing head motion—Several strategies can be implemented to reduce head motion artifacts in fMRI studies of younger children and severely ill youths who have difficulty staying still in the scanner. Patients and controls can be trained in a mock scanner with simulated sounds and confinement, and also with biofeedback training to reduce head motion as subjects perform tasks of interest. If there is high degree of motion that is not reduced with training, imaging study data are not likely to be useful. Training videos can be made available to prepare subjects to perform tasks they will perform in fMRI studies before scan sessions, to ensure that they understand the nature of task they will be asked to perform. Software can correct for head movement to some degree, but as head motion increases from 0.5 to 1 voxel width dimension and beyond, this correction becomes progressively inadequate and apparent activation effects are reduced. This is obviously a concern in clinical pediatric studies where patients might be

expected to have more difficulty remaining still for studies that typically take around 6-8 minutes. Because head motion could cause an underestimation of activation effects leading to a false inference of regional brain dysfunction, and thus is an issue that requires careful attention.

IX. Multimodal Imaging

IX.a. Application of High Density EEG in Pediatric Research—High density EEG is electromagnetic non-invasive source imaging that helps localize activation pattern with improving spatial resolution but high temporal resolution using a large number of electrodes on the scalp (64, 128 or 256 electrodes). EEG techniques provide event-related potentials (ERP) to discern the precise timing of neural system responses as subjects perform the sequence of cognitive steps needed to perform cognitive paradigms. Compared to fMRI, high density EEG studies provide greater opportunity to monitor the timing of task-related cognitive processing, and its integration across the brain, although with less ability to precisely localize the source of the signal in the brain especially in deeper brain structures.

In previous EEG studies, a visual Stop Signal Task showed a sharp negative component (N200) in healthy youth in inferior frontal cortex that corresponded with successful inhibition when a “Stop” signal cue was used to prevent a preplanned behavioral response. This N200 is attenuated in ADHD,⁸³ a finding that was replicated using an auditory Stop Signal Task.⁸⁴ Further, ERP evoked by Stop Signals differed for successful inhibitions compared to failed inhibitions.⁸⁵ There was greater amplitude of positive wave peaking around 320 msec over anterior medial frontal scalp (P3a) in healthy controls. This “success” related P3a activity is reduced in ADHD. Further, the error related negativity (ERN), a sharp negative wave that is present selectively on error trials, peaking 100 ms after motor response onset and distributed over anterior medial frontal cortex, has also been found to be reduced in ADHD.⁸⁶ Treating maturational disturbances in impulse control such as that seen in these studies is a common target in child psychiatry. However, little data exists about how these findings are related to treatment status or illness severity, and about development effects in these cognitive ERPs, but this is a promising noninvasive and relatively low-cost approach for learning about brain system function in children and adolescence. Localizing the dysfunctions in brain regions that cause cognitive and emotional disorders, understanding the temporal dynamics of complex cortical circuitry, and improving knowledge about how available drug treatments normalize brain systems or fail to do so, are all research targets that will be greatly enhanced by EEG studies. Combining EEG studies with fMRI and behavioral studies will allow us to reap the benefits of the multi-modal technologies becoming available in modern medicine.

IX.b. Morphometric and Diffusion Tensor Imaging—Morphometric studies are another approach that may be useful in pediatric research. Diffusion tensor imaging is an anatomic technique that is an effective way to capture maturational changes in brain white matter that serves as a crucial substrate for the connectivity of component nodes in neural systems. Studies are in progress that use basic parameters such as fractional anisotropy (FA) and increased apparent diffusion coefficient (ADC) in a region of interest to define these values across the entire white matter fiber tracts connecting various regions in the affected circuitry in disorders such as PBD.⁸⁷ Using this approach, fiber tracts such as the anterior corona radiata (ACR), inferior longitudinal fasciculus (ILF) and superior longitudinal fasciculus (SLF) can be characterized in terms of axonal organization and/or integrity, myelination, and fiber tract coherence. Large scale studies to model age and gender effects on these parameters are underway in several laboratories. Possible advantages to these measurements include an ability to discover potential white matter problems that contribute to disorders, especially if they interfere with the functional connectivity across widely distributed brain systems to disrupt cognitive and affective functional circuitry.

IX.c. Pharmacogenetics—Neuroimaging, and fMRI in particular, can become an important tool in functional genomics. fMRI, as a direct assay of brain physiology, has revealed differences in information processing linked to functional genomic polymorphisms even when they are sufficiently modest to not interfere with observable behavioral performance.⁸⁸ Genetic polymorphisms related to serotonergic neurotransmission are related to activity measured in fMRI in the amygdala during emotional processing.⁸⁹ Polymorphisms in monoamine system genes affect prefrontal activity and working memory task performance in response to amphetamine.⁹⁰ As studies of this nature progress, fMRI studies have tremendous potential for learning about genetic aspects of disease processes and of responses to biological therapies. One line of work very early in its evolution is efforts to understand genetic predictors of how and to what extent brain systems are altered by drug therapies. This may provide important information about what is likely to be the most effective treatment and dose of a specific medication that can be tailored to an individual patient.

X. Clinical Translation: The Final Frontier

In summary, we propose a systems level integrative model encompassing cognitive and affective circuits to illustrate an important area of research related to and involving child psychiatry. We highlighted multiple dimensions that inform research methodology to achieve that goal while incrementally building our knowledge base of pediatric disorders. More specifically, to improve treatment of psychiatric illnesses in children and adolescents, we need to understand the nature of brain disturbances associated with the disorders and how medications affect these abnormalities. Innovative research programs are making steady progress toward identifying biomarkers of illness that may be useful for early intervention and perhaps prevention strategies. Similar studies are developing tools for monitoring treatment response that are beginning to clarify how drugs effect brain systems to facilitate clinical improvement. Such efforts may provide useful and objective tools to quickly distinguish effective vs ineffective treatment for individual patients. Such advances will facilitate the development and use of safe and informed early interventions that are a key to progress in pediatric medicine.

In the end, with growing and extensive knowledge from the animal literature and healthy human studies, disease models are being developed and elaborated that have great potential for improving clinical practice. Understanding brain dysfunctions in child psychiatric disorders at the level of functional brain systems can provide an important bridge from molecular and biochemical knowledge to clinical behavioral problems, with considerable benefit to translational research approaches and treatment development. Interdisciplinary work in this area involving psychologists building appropriate neurobehavioral paradigms, physicists, engineers and statisticians that provide technical and methodological expertise for brain imaging studies, together with child psychiatry investigators can greatly increase understanding of pathophysiology of pediatric disorders. This work can provide crucial new information about the mechanisms by which therapeutic interventions reduce the impact of pathophysiological processes on cognition and affect, and thereby guide development of ever better strategies for diagnosis and therapy in child psychiatry.

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AMG=Amygdala; CN=Caudate Nucleus; DACC=Dorsolateral Anterior Cingulate Cortex; DLPFC=Dorsolateral Prefrontal Cortex; VACC=Ventral Anterior Cingulate Cortex; VLPFC=Ventrolateral Prefrontal Cortex; OC=Occipital Cortex; Rt = right; Lt = left

1. Functional Brain Circuits in Pediatric Bipolar Disorder

Cognitive Circuitry shows the key link between the DLPFC and the caudate involved in attentional control, and the connection between the VLPFC and the caudate/ventral striatum implicated in response inhibition and attention. Fronto-limbic Affective Circuitry spanning from the VLPFC to amygdala participates in top-down regulation of emotion. Interfacing Circuitry illustrates the functional connectivity between cognitive regions (DLPFC and DACC) and affective regions (VLPFC and VACC/pregenual and subgenual ACC) at the level of PFC and the intermediary ACC; working in concert in healthy individuals. Face Response Circuitry connects the visual or occipital cortex with fusiform gyrus (not shown here) and the STS. The Occipito-limbic Associative Circuitry connects the occipital cortex to right amygdala, involved in fast or automatic processing of emotional/ facial stimuli.

2. Reduced Activation in the Prefrontal Cortex in Response to Negative Words in Pediatric Bipolar Disorder